The "Bottom-Up" Approach ~~to Estimating Low-Dose Risk Cannot Always Be Considered Conservative~~Does Not Necessarily Bound Low-Dose Risk.

Starr and Swenberg (2013) proposed a "bottom-up" modeling approach, the purpose of which is to bound low-dose cancer risks from chemicals that are found endogenously within the body and thus provide a reality check on risk estimates derived by traditional approaches used by Agencies such as the Environmental Protection Agency (EPA). The approach does not use ~~dose-response~~ tumor incidence dose-response data from laboratory animals or humans exposed at different doses for quantification, but relies only on the endogenous concentration level, C_0, of an internal metric in a specific tissue (e.g., N^2-hydroxymethyl-dG mono-adducts in several tissues in the case of formaldehyde) and the background risk, P_0, for the cancer type of interest. The ratio P_0/C_0 is used to estimate the average slope of the dose-response relationship between risk and the internal dose at low (exogenous) exposures, and an upper bound on this ratio is described as an "upper bound" on the low (exogenous) dose-response slope by virtue of the following procedures inherent in the approach: 1) for purposes of bounding, all of the background risk is assumed to be due to the endogenous internal dose (as measured, for example, by the endogenous adduct concentration), 2) the dose-response relationship for risk as a function of endogenous adduct concentration is assumed to be linear, and 3) a lower confidence limit, C_{0L}, on the estimate of the endogenous concentration, C_0, is used.

The purpose of this letter is to articulate why the proposed "bottom-up" approach ~~should not be considered always to~~does not necessarily "bound" ~~low dose risk. (the range of plausible risk estimates derived by more traditional approaches. We demonstrate a fundamental point, that flaw in this approach on account of which P_0/C_{0L} is not necessarily an upper bound. First, the approach is highly reliant on several assumptions such as that the appropriate internal moiety and site of initial action have been identified, estimates of internal dose are reasonably accurate, and the range of human variability in factors affecting pharmacokinetics or pharmacodynamics have been suitably considered. One or more of these assumptions could be wrong or incomplete, potentially affecting whether the procedure can bound the risk. However, even if all of these assumptions are correct, P_0/C_{0L} is not necessarily an upper bound. We focus here on the latter issue, which we believe is a fundamental flaw in this approach.~~

Figure 1 depicts the "bottom-up" approach graphically. The figure shows that if C_0 was accurately known, the approach could underestimate the dose-response slope at C_0 if the dose-response curve is concave upwards ~~in the vicinity of C_0~~in the endogenous exposure range. The dotted line with slope P_0/C_0 is the linear approximation used in the bottom-up approach to represent the average risk at zero exogenous exposures. The solid black curve in Figure 1 represents a plausible~~essible non-linear~~ dose-response relationship ~~that is sub-linear over the plotted range~~ (which, of course, is unobservable near and below C_0) ~~but would be "linear" at low external dose in that there is no threshold and for small changes from zero exogenous dose it is well approximated by a line with a nonzero slope.~~ It is clear from this figure that whenever the true dose-response relationship is upward curving ~~in the neighborhood of C_0~~ endogenous exposures, the linear assumption used in the "bottom-up" approach is not conservative in estimating slope or risk for nonzero external doses unless the underestimate inherent in extrapolating upward happened in a particular circumstance to be more than offset by an over-estimate due to some

Commented [VJ1]: It certainly can be, by some, under some conditions.

Commented [BD2R1]: I see you inserted the word "always". That helps make the point.

Alternatively, we could change to say that the process does not "bound"; but inserting "always" may make the point in a clearer way.

The approach estimates a dose-response for small changed in exogenous dose that might either over-estimate or under-estimate the actual change in risk for small changes in dose depending on how far off several assumptions are that go in opposite directions. As such, it is not a procedure that "bounds" – which is the claim of Starr et al. It is a sort of chimera. There is an aspect that is inherently anti-conservative for sublinear dose-response curves; and, there are some assumptions one might expect would be conservative (as in assuming all observed risk in the general population is due to the chemical being assessed.) The result is we don't from the procedure know if it is, or is not, conservative. Hence, it is not always conservative.

Commented [rs3R1]: "Bound" is a better and more precise term anyhow as opposed to the more colloquial ...

Commented [VJ4]: Check – the reference list shows 2012

Commented [BD5R4]: Good catch. Thee wrong date ...

Commented [VJ6]: Po is based on tumor incidence data ...

Commented [BD7R6]: We can clarify. ...

Commented [rs8R6]: I think "dose-response" does it. I ...

Commented [BD9R6]: Actually, I think John would argu ...

Commented [VJ10]: Are Starr and Swenberg arguing th ...

Commented [BD11R10]: I think Starr is arguing the ...

Commented [VJ12]: These assumptions are routine an ...

Commented [BD13R12]: Not sure I agree this is a ...

Commented [rs14R12]: John's remark had a strong ...

Commented [VJ15]: Are you sure you want to present ...

Commented [BD16R15]: We could substitute a figure ...

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Commented [BD17]: Tried adding new text to help the ...

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Commented [rs18]: David, I think this just confuses the ...

Commented [rs19R18]:

Commented [BD20R18]: I'm okay with RS suggestion ...

other assumption. Likewise, the upper bound on P_0/C_0 obtained by the use of the lower bound on C_0 is not necessarily an upper bound on the low-dose slope of the true dose-response relationship. The authors of the "bottom-up approach" have not provided a basis to conclude that usingtaking the lower confidence limit on C_0 or other "conservative assumptions" will necessarily overcome any underestimation by the "bottom-up" approach of the slope at C_0. They might overcome this underestimation, but from the procedure per se one would not know when that would, or would not, be the case.

Starr and Swenberg (2013) did not contend that the endogenous dose-response relationship was not upward curving, but instead they assume tacitly that a linear dose-response relationship over the endogenous range bounded the slope of all possible endogenous dose-response relationships. This is incorrect. But, as illustrated, wWhen a dose-response relationship is curved upwards, a line drawn from the origin to a point on the true dose-response curve to the origin will overestimate the risk for points below that upper point on the curve, within that interval but will maywill underestimate the risk for doses above that upper point on the curve. the slope at zero exogenous dose obtained from the Starr and Swenberg linear assumption will underestimate the slope at zero exogenous dose. AWhile there are good reason to assume a dose-response curve will be linear for very small changes in dose from any point on a smooth dose-response curve, aA sublinear dose-response relationship over the endogenous range is clearly plausible on biological grounds. For example, it is likely that baseline levels of DNA repair enzymes and other protective systems evolved to deal with endogenous DNA damage would work most effectively for lower levels of endogenous adducts.

Furthermore, the approach in Starr and Swenberg (2013) is highly reliant on several assumptions such as that the appropriate internal moiety and site of initial action have been identified, estimates of internal dose are reasonably accurate, and the range of human variability in factors affecting pharmacokinetics or pharmacodynamics have been suitably considered. One or more of these assumptions could be wrong or incomplete, potentially further impacting the ability of the procedure to bound risk.Because this approach inherently uses internal dose, it is more sensitive to these assumptions than are many estimates derived from related external dose to extra risk except those that utilize PBPK models for interspecies extrapolation.

The authors note that their approach is consistent with the concept of additivity to background disease processes (Crump et al. 1976) and that the upper bound on P_0/C_0 is directly comparable to the estimate derived from the linearized multistage model. It is useful to indicate that adherence to this concept of additivity does not require the globally linear constraint (i.e. linear all the way down to an origin at zero endogenous dose) imposed by the bottom-up approach but instead only requires local linearity in the proximity of zero exogenous dose.

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D. A. Bussard
C. Chen
J. Jinot

Commented [BD21]: Another try at heading off a simple rebuttal that "in this case, see, this data suggests the procedure was not conservative" as was done by Starr and EPA mtg on formaldehyde. To note that in any particular use, it might turn out not to be conservative; but, as a procedure, it is limited in one does not know if in that case it will be on balance conservative. You do know this one aspect is not conservative.

Commented [VJ22]: check

Commented [BD23R22]: 2013 is correct.

Commented [VJ24]: Seems a very strong statement, depends on how you draw the curves. If you relax the assumption of all background risk is due to endogenous exposure then various curves can be drawn that indicate overestimation of risk in the region below Co and possibly above Co depending on the curvature of the dose-response i.e. the lines will cross at some point, but it is not unreasonable to indicate some overestimation close to Co, hence the title is too strongly stated.

Commented [BD25R24]: That suggests an interesting expansion.

We could include an example of a case at which some of the background risk is not due to the chemical substance being analyzed. That could show that even in that case, the bottom-up approach can under-predict the slope at zero exogenous dose. One could have another version where even less of the background dose was due to the chemical in question and show that of course at some point the bottom-up approach could over-estimate the true slope.

Commented [rs26R24]: The approach is claimed to be conservative upper bound meaning that even in the worst case scenario it is an overestimate. It is NOT even billed a

Commented [VJ27]: These assumptions are routine and not specific to the Starr and Swenberg analysis; the range

Commented [BD28R27]: Not sure I agree this is a standard assumption. My perception is that for many chemicals we use external dose and our dose-response is

Commented [rs29R27]: John's remark had a strong impact on me even though I disagree that the assumptions are standard. Since the average reader of even the Starr

Commented [rs30]: I am fine with deleting this

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Commented [BD31]: Actually, rather that raising the idea those other aspects might well be wrong, perhaps it is better just to note the procedure is sensitivt to them. An

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Commented [rs32]: I am in favor of deleting this also. This will get the paper receiving a tangential set of comments such as what I have often heard in the context

R. Subramanian

References:

Crump, K.S., Hoel, D.G., Langley, H., Peto, R., 1976. Fundamental carcinogenic processes and their implications for low dose risk assessment. Cancer Res. 36, 2973–2979.

Starr, T. B., and Swenberg, J. A. (20132). A novel bottom-up approach to bounding low-dose human cancer risks from chemical exposures. Regul Toxicol Pharmacol 65(3), 311-5

Commented [VJ33]: check

Commented [BD34R33]: 2013! Thanks

Figure 1: Graphical Representation of the "Bottom-Up" Approach in a Case in Which the True Dose Response Curves Upward In the (Unobservable) Endogenous Range